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<p>(21) International Application Number: PCT/US98/13861 (22) International Filing Date: 2 July 1998 (02.07.98) (30) Priority Data: 60/051,711 3 July 1997 (03.07.97) US (71) Applicants: NEUROGEN CORPORATION [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). PFIZER INC. [US/US]; East 42nd Street, New York, NY 10017 (US). (72) Inventors: THURKAUF, Andrew; 16 Fox Den Road, Danbury, CT 06811 (US). YUAN, Jun; 26 Cedar Road, Clinton, CT 06413 (US). HUTCHISON, Alan; 29 Kimberly Lane, Madison, CT 06443 (US). BLUM, Charles, A.; 785 W. Pond Meadow Road, Westbrook, CT 06333 (US). ELLIOT, Richard, L.; 1 Applewood Common, East Lyme, CT 06498 (US). HAMMOND, Marlys; 85 Sullivan Road, Salem, CT 06420 (US). (74) Agents: RICHARDS, John; Ladas &amp; Parry, 26 West 61st Street, New York, NY 10023 (US) et al.</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>
<p>(54) Title: CERTAIN DIARYLIMIDAZOLE DERIVATIVES; A NEW CLASS OF NPY SPECIFIC LIGANDS</p> <p>(57) Abstract</p> <p>Certain diarylimidazoles act as partial agonists or antagonists for NPY receptors, in particular NPY 5 receptors. They are of use, for example in treating loss of appetite. Such compounds bear aryl groups in the 2 position. Many of the compounds are novel.</p> <div data-bbox="1003 1837 1445 1948" style="text-align: right;"><p>Applicants: Mohammad R. Marzabadi et al. U.S. Serial No.: 10/019,881 Filed: December 27, 2001 Exhibit P</p></div>		

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CERTAIN DIARYLIMIDAZOLE DERIVATIVES;  
A NEW CLASS OF NPY SPECIFIC LIGANDS  
RELATED APPLICATION

This application claims priority from provisional application 60/051711  
5 filed on July 3, 1997.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to pharmaceutical compositions containing certain  
diarylimidazole derivatives which selectively bind to human NPY receptors. Some of  
10 such diarylimidazoles are believed to be novel. The invention further relates to the use  
of such compounds in treating feeding disorders such as obesity and bulimia as well as  
certain cardiovascular diseases such as essential hypertension.

Prior Art

Neuropeptides known as Neuropeptide Y (NPY) are believed to have a  
15 role in a variety of functions in the body and in particular have been associated with  
stimulation of appetite but also to effect anxiolysis and regulation of coronary tone.  
Such compounds bind to a number of different receptor sites. U.S. Patent 5,571,695  
(Selbie et al.) describes the genomic DNA sequences that code for the Y-1 receptor.  
U.S. Patent 5,554,621 (Poindexter et al.) describes certain 4-phenyl dihydropyridines  
20 that are NPY antagonists and noted the existence of at least five receptor subtypes for  
NPY. U.S. Patent 5,545,549 (Gerald et al) describes the human Y2 receptor and the  
DNA coding for it. U.S. Patent 5,516,653 (Bard et al.) describes the human Y4  
receptor and the DNA coding for it. U.S. Patent 5,602,024 (Gerald et al) describes  
the human Y5 receptor and the DNA coding for it. It states that this receptor seems to  
25 be the most significant for appetite stimulation.

Many diarylimidazoles are known for a variety of uses. For example,  
European Patent Publication 627499 (Shikoku Chemicals Corporation) and its United  
States equivalent, U. S. Patent 5,498,301 (Hirao) describe the use of 2,4-  
diphenylimidazole and 2,4-diphenyl-5-methyl imidazoles as water based surface  
30 treating agents for use on copper surfaces and compares their activity to that of 2,4,5-  
triphenylimidazole. The 2-phenyl group may be substituted by alkyl or halo groups  
and the 4-phenyl group by alkyl, halo, alkoxy, di-loweralkylamino, cyano or nitro

groups. Specific compounds mentioned in the United States Patent include 2-phenyl-4-(4-chlorophenyl)imidazole, 2-phenyl-4-(2,4-dichlorophenyl)imidazole, 2-phenyl-4-(4-bromophenyl)imidazole, 2-phenyl-4-(2-tolyl)imidazole, 2-phenyl-4-xylylimidazole, 2-(4-chlorophenyl)-4-phenylimidazole, 2-(4-bromophenyl)-4-phenylimidazole, 2-(2,4-dichlorophenyl)-4-phenylimidazole, 2-(4-tolyl)-4-phenylimidazole, 2-(4-methoxyphenyl)-4-phenylimidazole, 2-(4-dimethylaminophenyl)-4-phenylimidazole, 2-(4-cyanophenyl)-4-phenylimidazole, 2-(3-nitrophenyl)-4-phenylimidazole, 2-(2,4-xylyl)-4-phenylimidazole, 2-(4-chlorophenyl)-4-(4-chlorophenyl)imidazole, 2-(2,4-dichlorophenyl)-4-(2-tolyl)imidazole, 2-(2-bromophenyl)-4-(2,3-xylyl)imidazole, 2-(4-ethyl phenyl)-4-(2-chlorophenyl)imidazole, 2-(2-ethoxyphenyl)-4-(4-bromophenyl)imidazole, 2-(2-cyanophenyl)-4-(4-tolyl)imidazole, 2-(3-nitrophenyl)-4-(2,3-dichlorophenyl)imidazole, 2-(4-diethylaminophenyl)-4-(4-fluorophenyl)imidazole, 2-(4-chlorophenyl)-4-phenyl-5-methylimidazole, 2-(4-tolyl)-4-phenyl-5-methylimidazole, 2-(2,4-dichlorophenyl)-4-phenyl-5-methylimidazole, 2-(2,3-xylyl)-4-phenyl-5-methylimidazole, 2-(4-methoxyphenyl)-4-phenyl-5-methylimidazole, 2-(4-dimethylaminophenyl)-4-phenyl-5-methylimidazole, 2-(2-nitrophenyl)-4-phenyl-5-methylimidazole, 2-(3-cyanophenyl)-4-(4-chlorophenyl)-5-methylimidazole, 2-(2-nitrophenyl)-4-phenyl-5-methylimidazole, 2-(3-cyanophenyl)-4-(4-chlorophenyl)-5-methylimidazole.

20 PCT Publication WO 95/04274 (Nippon Soda Co. Ltd.) describes the use of a wide range of imidazoles for pest control including 2-(optionally halogenated)phenyl-4-(optionally halogenated) phenylimidazoles.

Suzuki et al. in Chem. Pharm. Bull (1986) 34, 3111-20 describe the synthesis of 2-aryl-4-(3-thienyl)imidazole derivatives of use as antiinflammatory agents.

25 U.S. Patent 5,017,467 describes 2,4-di(2-substituted aminophenyl)imidazoles wherein the 5 position is optionally substituted by a group capable of being split off by reaction with an oxidized product of a color developing agent for use as a cyan coupler in photography.

East German patent publication 299059 (Chemical Abstracts 117:131199) describes 2-(2-hydroxyphenyl)-4-substituted imidazoles wherein the substituent in the 4 position may be an optionally substituted phenyl group and the 5 position may be substituted by a phenyl or alkyl group.

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East German patent publication 297816 (Chemical Abstracts 116:214504) describes 2-arylimidazole compounds wherein the 4 or 5 positions may have aryl substituents of use as lipoygenase inhibitors.

German Patent Publication 3917677 (Chemical Abstracts 115:25542) describes 2-(4-hydroxy-3,5-di-tert.-butyl)phenyl-4-(4-dialkylamino)phenylimidazoles of use as chromogenic substrates in analytical redox reactions. The 4-phenyl group and the 5 position of the imidazole ring may be further substituted by alkyl groups.

German Patent Publication 3411997 (Chemical Abstracts 104:145136) describes compounds of use as redox indicators including 2-(substituted phenyl)-4-(substituted phenyl) imidazoles.

Soviet Patent Publication 1051076 (Chemical Abstracts 101:90924) describes 2-phenyl-4-(phenyl or p-tolyl)imidazoles which may be methyl- or phenyl-substituted in the 5 position.

European Patent Publication 0131973 (Instituto de Angeli S. p. A.) describes the use of certain aryl imidazoles, including 2-phenyl-4-(4-nitro-phenyl)-1H-imidazole and 2-phenyl-4-(4-amino-phenyl)-1H-imidazole as intermediates in the production of amidines useful as H<sub>2</sub> receptor blocking agents.

U. S. Patents 4,757,124 and 4,758,639 (Koyangi et al ) describe the use of inter alia 2,4-diphenylimidazole for prevention of scaling of the walls of a polymerization vessel used in the production of vinyl polymers.

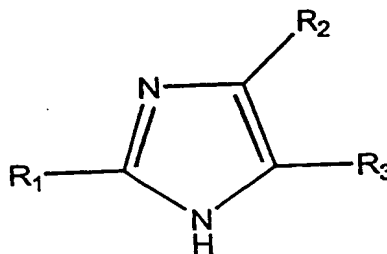
Other compounds found in the course of database searches include: 4-(2,4-dichlorophenyl)-2-phenyl-5-methylimidazole; 2,4-bis-(2,4-dichlorophenyl)-imidazole (C.A. Registry No 197514-18-4); 2-(4-methoxyphenyl)-2-(2-aminophenyl)imidazole (C.A. Registry No 197011-25-9); 2-(4-methoxyphenyl)-2-(2-trifluoromethylphenyl)imidazole (C.A. Registry No 174356-09-3); 4-(2-ethylaminophenyl)-2-phenylimidazole (C.A. Registry 170448-20-1); N-[2-(2-phenyl-1H-imidazol-4-yl)-phenyl]acetamide (C.A. Registry 162706-94-7); 2-(4-chlorophenyl)-2-(3-trifluoromethylphenyl)imidazole (C.A. Registry 162701-76-0); N-[4-[2-(2-hydroxyphenyl)-1H-imidazol-4-yl]phenyl]acetamide (C. A. Registry 138500-29-5) and its methoxy homolog (C. A. Registry 138500-28-4); several 2-phenylimidazoles wherein the 4 position is substituted by a 3,3-dimethyl-2H-indole-2-one group (C. A. Registry Nos 135466-37-4, 135466-36-3; 135437-73-9; 135437-72-8; 135437-71-7;

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135437-68-2; 135437-66-0; 135437-65-9; 135437-64-8; 135437-63-7; 135437-62-6; 135437-61-5; 135437-60-4 and 135437-59-1); analogous 2(1H)-3,4-dihydroquinolones (C.A. Registry Nos 135437-70-6 and 135437-67-1), 2,4-bis-(2-aminophenyl)-imidazole (C.A. Registry No 131623-81-9); 4-(4-hydroxyphenyl)-2-phenylimidazole (C.A. Registry No 111273-30-4); 2,4-bis(4-phenoxyphenyl)imidazole (C.A. Registry 107783-02-8); 2,4-bis(bi-phenyl-4-yl)imidazole (C.A. Registry 106304-01-2); 4-(2-phenyl-1H-imidazol-4-yl)benzeneamine (C.A. Registry No.96139-68-3); various 2-(2-hydroxyphenyl) 4-(possibly substituted) phenylimidazoles having methyl, ethyl, butyl or phenyl substituents in the 5-position; and a number of more complicated structures.

### SUMMARY OF THE INVENTION

This invention provides pharmaceutical compositions comprising compounds of Formula I which interact with Neuropeptide Y receptors and in particular with NPY5 receptors and methods of treatment of conditions susceptible to such interactions. It further relates to the use of such compounds in treating feeding disorders such as obesity and bulimia as well as certain cardiovascular diseases such as essential hypertension. Suitable compounds are those of Formula I:



where R<sub>1</sub> is an unsubstituted or mono, di or trisubstituted aryl group wherein said aryl group is mono or bicyclic, in which case only the ring bound to the imidazole group ring need be aromatic, and said aryl group may be carbocyclic or contain up to 2 hetero atoms which may be nitrogen, oxygen or sulfur, and said substituents are selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl or alkoxy groups themselves may be substituted by an amino or mono- or di- alkyl amino group or an acyl group), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having

1-6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, mono or disubstituted carbamyl where the CO group is bound to the aryl group and wherein the substituents are lower alkyl or aryl lower alkyl, mono or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates or any 2 adjacent substituents on the aryl ring may be represented as  
5  $X(CH_2)_nY(CH_2)_mZ$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3.

One of  $R_2$  and  $R_3$  is selected from the group consisting of hydrogen, hydroxymethyl, alkoxymethyl having up to 6 carbon atoms in each alkoxy group,  
10 straight or branched chain lower alkyl having 1-6 carbon atoms, cyano, or a carboxylic or carboxylate ester group wherein the esterifying group typically contains up to six carbon atoms.

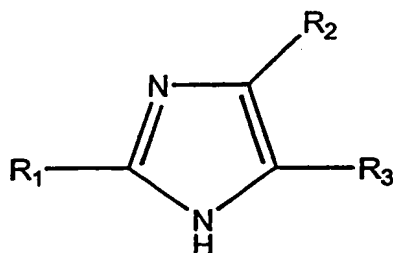
The other of  $R_2$  and  $R_3$  is an aryl group which is either unsubstituted or mono, di or trisubstituted wherein said aryl groups are mono or bicyclic (in which case  
15 only the ring bound to the imidazole grouping need be aromatic) and may be carbocyclic or contain up to 2 hetero atoms and said substituents are selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl or alkoxy groups themselves may be substituted by  
20 amino or a mono- or di- alkyl amino group or an acyl group), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms (said alkyl groups being optionally substituted with a hydroxy or amino group), mono- or disubstituted carbamyl where the CO group is bound to the aryl group and the  
25 substituents are lower alkyl or aryl lower alkyl, mono- or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates additionally any two adjacent substituents on the aryl ring may be represented as  $-X-(CH_2)_n-$   
 $Y(CH_2)_mZ$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3.

30 These compounds are selective partial agonists or antagonists at human NPY5 receptors and are useful in the diagnosis and treatment in mammals of feeding disorders such as obesity and bulimia as well as certain cardiovascular diseases such as

essential hypertension and congestive heart failure.

### DETAILED DESCRIPTION OF THE INVENTION

The compounds of use in the present invention can be described by general Formula:



where R<sub>1</sub> is an aryl group, which may be unsubstituted or mono, di or trisubstituted. The aryl groups from which R<sub>1</sub> may be selected are typically mono or bicyclic groups, in which case only the ring bound to the imidazole group need be aromatic, and may be carbocyclic or heterocyclic containing up to 4 hetero atoms but no more than 2

15 hetero atoms in each ring. Typically each ring of the aryl group is a five or six membered ring. Suitable aryl groups include phenyl, naphthyl, indanyl, pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, indolyl, benzofuranyl, thianaphthyl, isoindolyl, isobenzofuranyl, quinoliny, isoquinoliny, quinazoliny, indazolyl, quinoxaliny, cinnoliny 1,2,3,4-tetrahydroquinoliny, 2,3-dihydroindolyl, phenomorpholiny, 20 benzodioxaziny, phenothiomorpholiny and methylenedioxyphenyl groups. Suitable substituents include: halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, which alkyl and alkoxy groups themselves may be substituted by an amino or a mono- or di-alkylamino group or a mono- or di-alkaryl group such as 25 benzyl or by an acyl group, straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups such as alkanoyloxy groups of from 2 to 7 carbon atoms, such as acetoxy, and aroyloxy groups such as benzoyloxy, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, mono or 30 disubstituted carbamyl groups wherein the substituent is lower alkyl or aryl lower alkyl, mono or disubstituted carbamyl where the CO group is bound to the aryl ring and the substituents are lower alkyl or aryl lower alkyl, carbamates such as mono- or



di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates such as methyl phenyl carbamate and diphenyl carbamate. In addition any two adjacent substituents may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3.

One of  $R_2$  and  $R_3$  is selected from hydrogen, hydroxymethyl, alkoxy-methyl having from 1 to 6 carbon atoms in the alkyl group, straight or branched chain lower alkyl having 1-6 carbon atoms, cyano, or a carboxylic or carboxylate ester group wherein the esterifying group typically has up to six carbon atoms.

The other of  $R_2$  and  $R_3$  is an aryl group either unsubstituted or mono, di or trisubstituted. Suitable aryl groups are mono or bicyclic and may be carbocyclic or contain up to 2 hetero atoms. They include phenyl, naphthyl, indanyl, pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, indolyl, benzofuranyl, thianaphthenyl, isoindolyl, isobenzofuranyl, quinoliny, isoquinoliny, quinazoliny, indazole, quinoxaliny, cinnoliny, 1,2,3,4-tetrahydroquinoliny, 2,3-dihydroindolyl, phenomorpholiny, benzodioxaziny, phenothiomorpholiny and methylenedioxyphenyl groups. Suitable substituents include: halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, (which alkyl or alkoxy groups may be substituted with an amino or a mono- or dialkyl amino group or a mono- or di-alkaryl amino group or an acyl group), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyl groups such as acetyl, acyloxy groups such as alkanoyloxy groups of from 2 to 7 carbon atoms, such as acetoxy, and aroyloxy groups such as benzoyloxy, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms, said all groups being optionally substituted with a hydroxy or amino group, mono or di substituted carbamyl groups wherein the CO group is bound to the aryl group and the substituents are lower alkyl or aryl lower alkyl, carbamates such as mono- or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates such as methyl phenyl carbamate and diphenyl carbamate. In addition any two adjacent substituents may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3.

When used herein the term "alkyl" includes branched and straight chain alkyl groups and cycloalkyl groups. Such alkyl groups may be interrupted by an oxygen or sulfur atom. "Alkyl" further comprises groups containing both a cyclic and an acyclic portion. In the absence of any indication to the contrary, alkyl groups referred to in this application have from 1 to 8 carbon atoms and any cyclo alkyl group or portion of an alkyl group will have from three to six carbon atoms in the ring and may optionally contain some unsaturation. A "lower alkyl" group is an alkyl group as just defined containing up to six carbon atoms. "Acyl" groups may contain alkyl, aryl or aralkyl groups but normally no more than 8 carbon atoms. The term "alkaryl" is used to denote groups such as benzyl and phenylethyl groups. It will be recognized by those skilled in the art that several of the compounds of use in the present invention may exist in tautomeric form. In such cases, reference to a particular compound encompasses both tautomeric forms.

Particularly useful classes of compounds according to the present invention include those wherein the aryl group of  $R_1$  is selected from aryl monocyclic groups which may be carbocyclic or contain up to two hetero atoms (N, O, or S) and is either unsubstituted or is substituted by up to three groups such as halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl of 1- 6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, mono or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates. Additionally any 2 adjacent substituents on an aryl ring may be represented as  $-X(CH_2)_n-Y-(CH_2)_m-Z-$  where X Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3. For example  $R_1$  can most usefully be a phenyl, 4-fluorophenyl, pyridin-2-yl or a thiophene group.

Similarly, particularly useful non-aryl  $R_2$  and  $R_3$  groups include hydrogen, alkyl (as defined above).

Particularly useful aryl groups for  $R_2$  or  $R_3$  include as phenyl, thienyl, pyridyl, and naphthyl for example bearing up to three substituents selected from halo

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(especially chloro or fluoro), alkoxy (such as methoxy) and alkyl (such as methyl, ethyl groups. Particularly preferred groups include 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 4-chlorophenyl, 4-fluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxy-2-fluorophenyl, 4-ethoxy-2-fluorophenyl, 3-fluoro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 3-acetylphenyl, naphthyl, 1,4-benzodioxan-6-yl and benzo [b] morpholinyl, 4-alkyl (e.g. methyl, ethyl or n-propyl) benzo[b]morpholinyl, 4-alkyl.-2H,3H,4H-benzo[e]1,4-thiazinyl, 3-methylaminophenyl, 4-dimethylaminophenyl, 3-ethylaminophenyl, 3-(2-methylbutylaminomethyl)phenyl, 3-(ethylbutylaminomethyl)phenyl, 3(1,2-dimethylpropylaminomethyl)phenyl, 3-[(3-cyclohexyl-1-phenylpropyl)methylaminomethyl]phenyl, 3-[(2-cyclohex-1-enylethyl)aminomethyl]phenyl, 3-[(3-methylethoxy) propylaminomethyl]phenyl, 3-(tert.-butylaminomethyl)phenyl, 3-[methyl-(1-phenylpropyl)aminomethyl]phenyl, 3-(methylethylaminomethyl)phenyl and 3-[(4-methylphenyl)metylaminomethyl]phenyl.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic, mesylate and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Many of the compounds of use in the compositions of the present invention are believed to be novel. We are, however, aware of prior disclosures of compounds wherein

1)  $R_1$  and whichever of  $R_2$  and  $R_3$  is aryl are both phenyl, a bromophenyl group, a chlorophenyl group, 2,4-dichlorophenyl, a cyanophenyl group, 2-methoxyphenyl, 3-aminophenyl, 4-aminophenyl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-acetylaminophenyl, 4-phenoxyphenyl or biphenyl;

2) when  $R_1$  is phenyl, whichever of  $R_2$  and  $R_3$  is aryl is 2-acetylaminophenyl, chlorophenyl, biphenyl, 4-aminophenyl, p-tolyl, xylyl, 4-methoxyphenyl, 4-dimethylaminophenyl, 4-bromophenyl or 4-hydroxy-2,5-di-tert.-butylphenyl,

3) when one of  $R_2$  or  $R_3$  is phenyl,  $R_1$  is 2-hydroxyphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 4-chlorophenyl, biphenyl, 2,4-dichlorophenyl, 2,4-xylyl, 4-cyanophenyl or 6-quinolyl; and

- 4) R<sub>1</sub> is 2-hydroxyphenyl when R<sub>2</sub> or R<sub>3</sub> is p-tolyl, R<sub>1</sub> is 4-hydroxy-3-methoxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 4-dimethylaminophenyl; R<sub>1</sub> is 4-hydroxy-3,5-dimethoxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 4-aminophenyl; R<sub>1</sub> is 4-hydroxy-3,5-di-tert-butylphenyl when R<sub>2</sub> or R<sub>3</sub> is 4-hydroxyphenyl; R<sub>1</sub> is 4-chlorophenyl when R<sub>2</sub> or R<sub>3</sub> is 3-trifluoromethylphenyl; R<sub>1</sub> is 2-hydroxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 2- or 4-acetamidophenyl; R<sub>1</sub> is 2-methoxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 4-acetamidophenyl; R<sub>1</sub> is 2-ethoxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 2-acetamidophenyl; R<sub>1</sub> is 4-methoxyphenyl when R<sub>2</sub> or R<sub>3</sub> is 2-aminophenyl or 2-trifluorophenyl; R<sub>1</sub> is 2-aminophenyl when R<sub>2</sub> or R<sub>3</sub> is 2-iso-propylcarbonylphenyl or 5-acetamido-2-hydroxyphenyl, R<sub>1</sub> is 2-cyanophenyl when R<sub>2</sub> or R<sub>3</sub> is 4-tolyl, R<sub>1</sub> is 2-bromophenyl when R<sub>2</sub> or R<sub>3</sub> is 2,3-xylyl, R<sub>1</sub> is 3-cyanophenyl when R<sub>2</sub> or R<sub>3</sub> is 4-chlorophenyl and R<sub>1</sub> is 4-dimethylamino when R<sub>2</sub> or R<sub>3</sub> is an ester of 3-methoxy 4-hydroxyphenyl or 3,5-dimethoxy-4-acetoxyphenyl.

Among the compounds we believe to be novel are diarylimidazoles of the above formula wherein R<sub>1</sub> is 4-fluorophenyl, those wherein R<sub>2</sub> or R<sub>3</sub> is an N-substituted aminomethylphenyl group or is selected from the group consisting of naphthyl, cyanophenyl, N-substituted benzo[b]morpholine, 2H,3H-benzo[e]1,4-dioxin and N-substituted 2H,3H, 4H-benzo[e]1,4-thiazine.

Compounds according to the invention include: 2(4-fluorophenyl)-4-(4-methoxyphenyl)imidazole hydrochloride, 2-(thienyl-2-yl)-4-(4-chlorophenyl)imidazole, 2-(4-fluorophenyl)-4-(4-chlorophenyl)imidazole hydrochloride, 2-phenyl-4-(3-fluoro-4-methoxyphenyl)imidazole hydrochloride.

The pharmaceutical utility of compounds of this invention are indicated by the following assays for human NPY receptor activity.

#### Assays for Human NPY receptor binding activity

##### SKNMC Binding Assay

The procedure used is similar to that described by Gordon et al. (J. Neurochem. 55:506- 513, 1990). SK-M-MC cells were purchased from ATCC (Rockville, MD). Cells were maintained at 37°C and 5% CO<sub>2</sub> in Dulbecco's modified essential media (DMEM) with L glutamine and 110 mg/L sodium pyruvate, which was supplemented with 10% fetal bovine serum and 25 mM HEPES (pH 7.3). The binding assay was performed in 24-well plates (Falcon) when the cells were confluent. Taking care to not disturb the cells on the bottom of the wells, the media was aspirated, and

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0.5 ml of Dulbecco's phosphate buffered saline (DPBS) with calcium and magnesium were added to each well. The DPBS was aspirated and an additional aliquot of DPBS was added and aspirated. To begin the assay, binding buffer consisting of serum-free DMEM containing 0.5% bovine serum albumin, 0.1% bacitracin and 0.1 mM phenylmethylsulfonylfluoride was added to each well. The cells, the binding buffer, the drug dilution and [<sup>125</sup>I]PYY (MEM-DuPont: 50000-75000 cpm 50pM) were added to yield a final volume of 250 µl. Nonspecific binding was defined with 1 µM NPY (porcine or human, Bachem California). After a 2 hour incubation at room temperature, the plates were then put on ice and the wells were aspirated. The cells were washed twice with 0.5 ml of ice-cold DPBS. A dilute solution of Triton X-100 (1%) was then added to each well. After approximately twenty minutes at room temperature, an aliquot from each well was transferred to a 12x75 mm test tube, and the amount of [<sup>125</sup>I] was quantitated on a gamma counter with an efficiency of 80-85% (Genesys 5000, Laboratory Technologies). IC<sub>50</sub> values were calculated with the non-linear curve fitting program RS/1 (SigmaPlot, Jandel).

[<sup>125</sup>I]Binding at Human NPY Receptors Expressed in Sf9 Cells

Baculovirus-infected Sf9 cells expressing recombinant human NPY 5 receptors are harvested at 48 hours. At the time of harvest, cell pellets are resuspended in lysis buffer (20 mM Tris-HCl pH 7.4, 5 mM EDTA, 0.5 µg/ml leupeptin, 2 µg/ml Aprotinin and 200 mM PMSF) and homogenized using a Polytron (setting 3,25-30 seconds). Homogenates are centrifuged at 4 °C for 5 minutes at 200 x g (~1.5 rpm) to pellet the nuclei. The supernatant is collected into a fresh tube and centrifuged at 48,000 x g for 10 minutes. Pellets are washed once in lysis buffer and centrifuged. The final pellet is resuspended in PBS and stored in aliquots at -80 °C. Purified membranes are washed using PBS and resuspended in binding buffer (50 mM Tris(HCl), pH 7.4, 5 mM KCl, 120 mM NaCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 0.1% bovine serum albumin (BSA)). Membranes (20 µg/reaction tube) are added to polypropylene tubes containing 0.050 nM [<sup>125</sup>I]PYY(porcine), displacers ranging from 10<sup>-12</sup> M to 10<sup>-5</sup> M, and buffer to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 µM NPY(human) and accounts for 10% of total binding. Following a 2 hour incubation at room temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked GF/C Whatman filters (1.0%

polyethylenimine) and rinsed 2 times with 5 mLs cold binding buffer without BSA. A gamma counter is used to count filters with a n efficiency of 85%. IC<sub>50</sub> values were calculated with the non-linear curve fitting program RS/1 (Sigma Plot, Jandel).

The compounds of general formula I may be administered orally,  
5 topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intra sternal injection or infusion techniques. In addition,  
10 there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets,  
15 troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of  
20 sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non -toxic pharmaceutically acceptable excipient which are suitable for the manufacture of tablets. These excipient may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or  
25 sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a  
30 longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules

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wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

5           Aqueous suspensions contain the active materials in admixture with excipient suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl cellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for  
10           example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of  
15           ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

20           Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin. or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide  
25           palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

          Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable  
30           dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipient, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

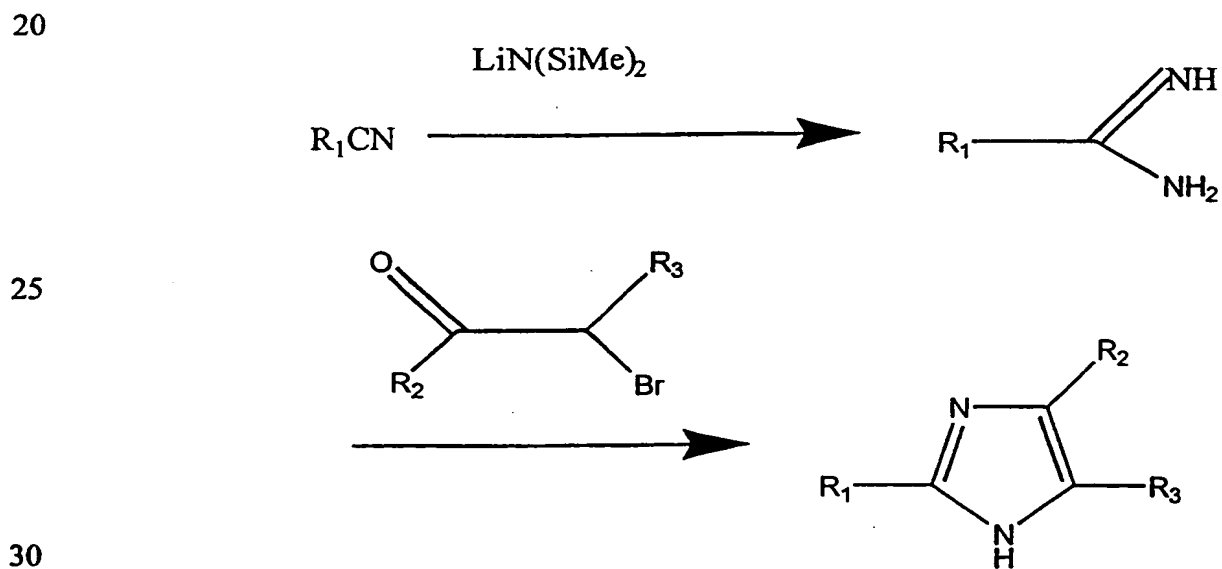


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Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. Dosages to be used will depend upon the particular use to which the composition is to be used.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

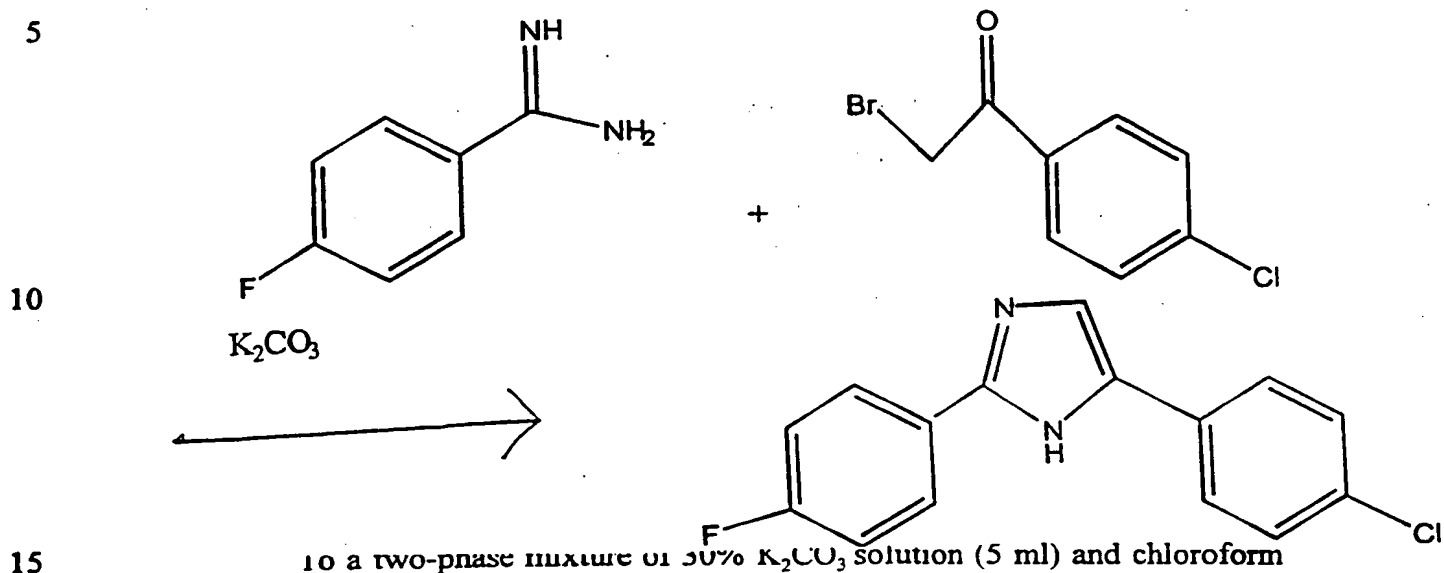
An illustration of the preparation of compounds of the present invention is given in Scheme I. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.

Scheme 1

where  $R_1$ ,  $R_2$  and  $R_3$  are as defined above.

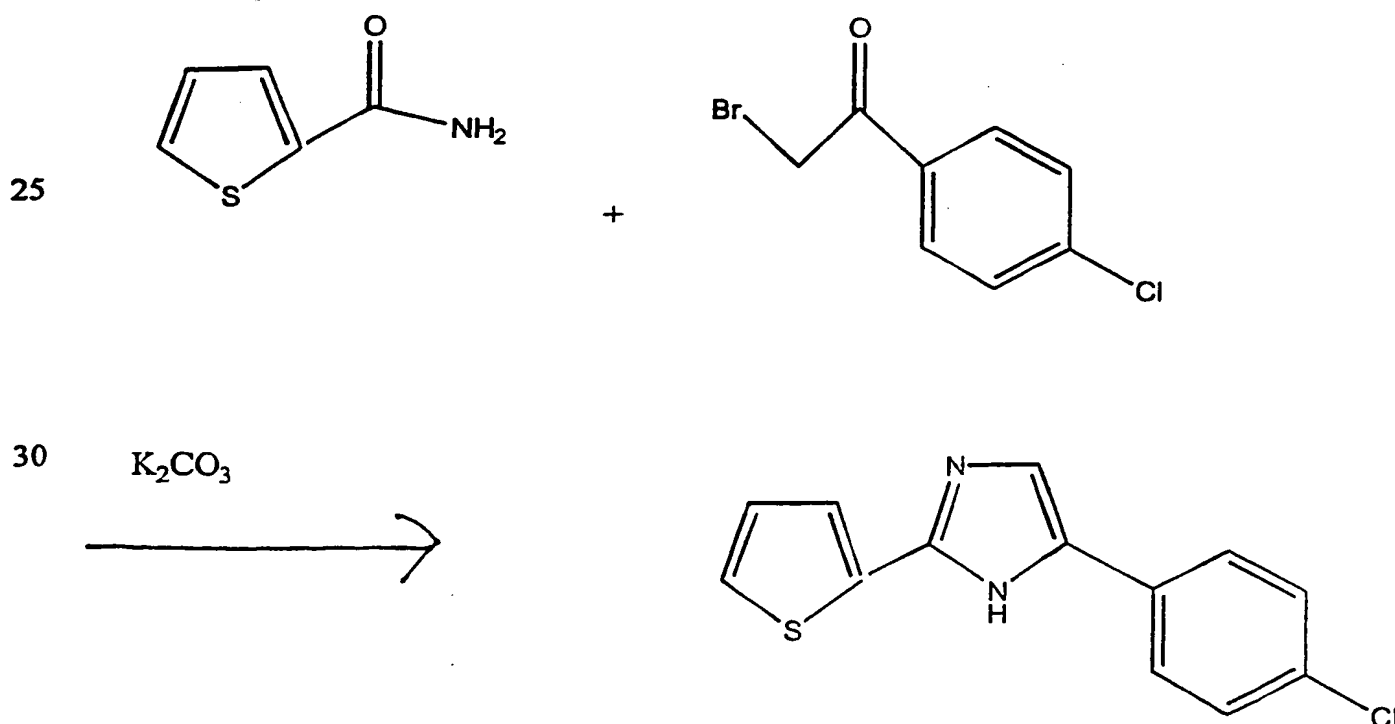
The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example 1



10 a two-phase mixture of 50%  $K_2CO_3$  solution (5 ml) and chloroform (5 mL) containing 276 mg of 4-fluorobenzamidine was added a solution of 468 mg of 2-bromo-4'-chloroacetophenone in chloroform (3 mL). After stirring for 1 hr, the reaction mixture was filtered. The white crystalline solid was washed with distilled water and dried in a vacuum oven overnight to afford 2-(4-fluorophenyl)-4-(4-chlorophenyl)imidazole (Compound 1).

Example 2



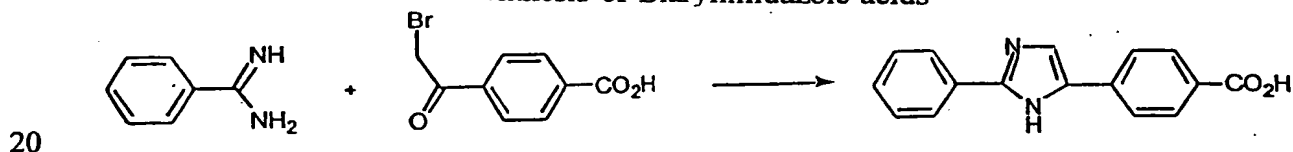
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To a solution of 2-cyanothiophene (10.9 g) in anhydrous diethyl ether (200 mL) was added solid lithium bis(trimethylsilyl)amide (24 g). After 30 min the stirred reaction was cooled in ice and 2 N HCl solution was added dropwise until the mixture was acidic to pH paper. The reaction was stirred for an additional 30 min and transferred to a separator funnel. The acidic extract was separated and the ethereal layer was discarded. The acidic aqueous layer was returned to the separator funnel, basified with 10 N NaOH solution and extracted with chloroform (2 X 150 mL). The organic extracts were dried over - potassium carbonate, filtered and concentrated to provide the desired 2-thienyl carboxamidine (8 g) as an orange solid.

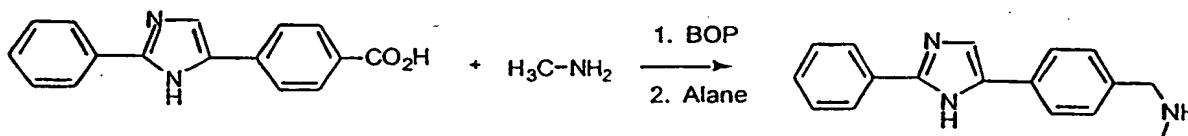
To a two-phase mixture of 30%  $K_2CO_3$  (5 ml) and chloroform (5 mL) containing 126mg of thiophen-2-yl carboxamidine was added a solution of 233 mg of 2-bromo-4'-chloroacetophenone in 3 ml of chloroform. After stirring for 1 h, the organic layer was dried ( $Na_2SO_4$ ) and concentrated. Purification on preparative TLC (5% MeOH/ $CH_2Cl_2$ ) afforded 2-(2thienyl)-4-(4-chlorophenyl)imidazole (Compound 2).

### Example 3

#### Synthesis of Biarylimidazole acids



To a mixture of the bromoacid (2.00 g, 8.20 mmol, 1.0 equiv) in THF (200 mL) was added the benzamidine free base (4.92 g, 41.0 mmol, 5.0 equiv) as a solid. After stirring at room temperature for 15 minutes, the mixture was evaporated, and the crude product was purified by flash chromatography (95% EtOAc, 5% MeOH) to afford the biphenylimidazole acid as a colorless solid.



To 0.1 mL of a 0.2M solution of the acid in 95% toluene/5% N-methylmorpholine was added 0.1 mL of a solution of 0.2M methylamine in 95% toluene/5% N-methylmorpholine, followed by 0.15 mL of a 0.2M solution of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium-hexafluorophosphate (BOP) in

dichloromethane, and the mixture was stirred at room temperature for 2 h.

Chromatography (1 g silica gel, EtOAc) afforded the amide as a yellow oil which was immediately reduced by adding 0.4 mL of a 0.5M alane dimethylethylamine complex in toluene. This mixture was stirred at room temperature for 2 hours, then was  
5 dissolved in ethyl acetate and washed with 1M NaOH and evaporated to provide the amine.

Particularly preferred compounds include:

- 4-(4-fluorophenyl)-2-phenylimidazole
- 2-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene
- 10 4-ethoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene
- 4-methoxy-3-fluoro-1-(2-phenylimidazol-4-yl)benzene
- 3-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene
- 3-methoxy-1-(2-phenylimidazol-4-yl)benzene
- 2-methyl-1-(2-phenylimidazol-4-yl)benzene
- 15 4-[2-(4-methoxyphenyl)imidazol-4-yl]-1-chlorobenzene
- 4-methoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene
- 4-(4-chlorophenyl)-2-phenylimidazole
- 4-(4-methylphenyl)-2-phenylimidazole
- 4-(4-methoxyphenyl)-2-phenylimidazole
- 20 4-(3-bromophenyl)-2-phenylimidazole
- 1-[3-(2-phenylimidazol-4-yl)phenyl]ethan-1-one
- 4-(4-bromophenyl)-2-phenylimidazole
- 4-(3-cyanophenyl)-2-phenylimidazole
- 4-(3-cyanophenyl)-2-(4-fluorophenyl)imidazole
- 25 4-(4-cyanophenyl)-2-phenylimidazole
- N-[3-(2-phenylimidazol-4-yl)phenyl]acetamide
- ethyl 2,4-diphenylimidazole-5-carboxylate
- (2,4-diphenylimidazol-5-yl)methan-1-ol
- 2-(4-fluorophenyl)-5-methyl-4-phenylimidazole
- 30 4-[2-(2-fluorophenyl)imidazol-4-yl]-1-chlorobenzene
- 4-(2-naphthyl)-2-imidazole
- 6-(2-phenylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin

- 6-[(2-(4-fluorophenyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
 6-{2-[4-trifluoromethyl]phenyl}imidazol-4-yl}-2H,3H-benzo[e]1,4dioxin  
 6-[(2-(4-fluorophenyl)-5-methylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
 6-(2-2-pyridyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
 5 6-(2-phenylimidazol-4-yl)benzo[b]morpholine  
 4-methyl-6-{2-phenylimidazol-4-yl}benzo[b]morpholine  
 4-propyl-7-{2-phenylimidazol-4-yl}benzo[b]morpholine  
 6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine  
 6-[2-(4-fluorophenyl)imidazol-4-yl]-4-methylbenzo[b]morpholine  
 10 4-ethyl-6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine  
 6-[2-(4-fluorophenyl)imidazol-4-yl]-2H,3H,4H-benzo[e]1,4-thiazine  
 4-methyl-6-[2-(4-fluorophenyl)imidazol-4-yl]-2H,3H,4H-benzo[e]1,4-thiazine  
 4-(4-chlorophenyl)-2-(2-pyridyl)imidazole  
 2-[4-(4-chlorophenyl)imidazol-2-yl]pyrazine  
 15 4-[2-(4-fluorophenyl)imidazol-4-yl]chlorobenzene  
 2-indole-3-yl-5-methyl-4-phenylimidazole  
 2-[4-(4-chlorophenyl)imidazol-2-yl]thiophene  
 4-(6-chloro(2-pyridyl)-2-phenylimidazole  
 dimethyl[2-(2-phenylimidazol-4-yl)(4-pyridyl)]amine  
 20 [3-(2-phenylimidazol-4-yl)phenyl]methylaniline  
 {3-[2-(4-fluorophenyl)imidazol-4-yl]phenyl}methylaniline  
 methyl[3-(2-phenylimidazol-4-yl)phenyl]methyl}amine  
 dimethyl[3-(2-phenylimidazol-4-yl)phenyl]methyl}amine  
 methyl[4-(2-phenylimidazol-4-yl)phenyl]methyl}amine  
 25 dimethyl[4-(2-phenylimidazol-4-yl)phenyl]methyl}amine  
 ethyl[3-(2-phenylimidazol-4-yl)phenyl]amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylbutyl)amine  
 (ethylbutyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 (1,2-dimethylpropyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]methyl}amine  
 30 (3-cyclohexyl-1-phenylpropyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)methylbutyl)amine  
 (2-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine

- (2-cyclohex-1-enylethyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 (cyclohexylphenylmethyl)methyl{{3-[2-phenylimidazol-5-yl]phenyl}methyl}amine  
 ethyl(1-{3-[2-(4-fluorophenyl)imidazol-5-yl]-isopropyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[3-methylethoxy]propyl]amine  
 5 (tert-butyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 methyl{phenyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine  
 (tert-butyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (methylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[(4-methylphenyl)methyl]amine  
 10 (cyclohexylphenylmethyl)({3-[2-(4-fluorophenyl)imidazole-5-yl]phenyl}methyl)methylamine  
 cyclopentyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (methylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylpropyl)amine  
 15 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)pentylamine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(methylethyl)amine  
 cyclopropyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 cyclobutyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[2-(4-methylphenyl)ethyl]amine  
 20 hexyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)hexylamine  
 (1,1-dimethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 25 (2-cyclohexyl-1-phenylethyl)methyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 {{3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-phenylethyl)amine  
 (2-cyclopentyl-1-phenylethyl)methyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (2-cyclohex-1-enylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 30 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)benzylamine  
 (ethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 cyclobutyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl}amine

- (3-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 [2-(4-methylphenyl)ethyl]{[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 (3-cyclohexyl-1-phenylpropyl)([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl]methyl)methylamine  
 5 cyclopropyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 (1,2-dimethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 ethyl([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl]methyl)amine  
 ([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl]methyl)(3-methylbutyl)amine  
 ethyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 10 cyclohexyl([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl]methyl)amine  
 methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 pentyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 ([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl]methyl)dipropylamine  
 dibutyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine.

15 Such compounds have IC<sub>50</sub> values between 1 nM and 1 μM.

With the exception of 4-(4-methylphenyl)-2-phenylimidazole 4-(2-methylphenyl)-2-phenylimidazole, 4-(4-chlorophenyl)-2-phenylimidazole and 4-(4-bromophenyl)-2-phenylimidazole, all of the preferred compounds listed above are believed to be novel.

20 The activities of compounds according to the invention have been investigated in the above mentioned tests.

#### Food Deprivation Protocol

Subjects. Experimentally naive and experienced male Sprague Dawley rats (Sasco, St. Louis, MO) weighing between 210 and 310 g at the beginning of the  
 25 experiment are employed. The animals are housed in a temperature-controlled (22°C/12<sup>0</sup>) and humidity-controlled (40- 70%RH) animal facility with a 12h light: 12h dark lighting schedule. The lights are on from 0530 till 1730 daily. When not in the experimental protocol animals are allowed free access to food (Standard Rat Chow, PMI Feeds Inc., #5012) and water. Animals are housed in stainless steel hanging home  
 30 cages in groups of two while not in the experimental protocol. For data collection, the animals are transferred to individual plastic metabolic cages located in the same room.

Apparatus. Consumption and elimination data are collected data are

collected while the animals are housed in Nalgene Metabolic Cages (Model #650-010). Each cage is comprised of subassemblies of clear polymethylpentene (PMP), polycarbonate (PC), and stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning.

5           The entire cylinder-shaped plastic and stainless steel cages rests on a stainless steel stand and houses one animal. The animal is contained in the round Upper Chamber (PC) assembly (12cm high and 20cm in diameter) and rests on a stainless steel floor (20cm diameter). Two subassemblies are attached to the Upper Chamber. The first subassembly consists of a 5.5. feeding chamber (10cm long, 5 cm  
10 high and 5 cm wide) with a PC feeding draw attached to the bottom. The feeding drawer has two compartments: A food storage compartment with a capacity for approximately 50 grams of pulverized rat chow and a food spillage compartment. The food storage compartment is distal to the Upper Chamber while the spillage compartment is proximal to the Upper Chamber. The animal is allowed access to the  
15 pulverized chow by an opening in the 55 floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment.

          The second subassembly adjacent to the Upper Chamber includes a water bottle support, a P.C. water bottle (100ml capacity) and a graduated water  
20 spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

          The lower chamber consists of a PMP Separating Cone, PMP collection funnel, PMP fluid (urine) collection tube (70ml capacity), and feces collection tube. The Separating Cone is attached to the top of the collection funnel which is attached to  
25 the bottom of the Upper Chamber. The urine runs off the Separating Cone onto the walls of the collection funnel and into the urine collection tub. The Separating Cone also separates the feces and funnels it into the feces Collection tube.

          A Ohaus portable Advanced Scale (I 0.1 g accuracy) is used to weigh the rats, food and water contains, and the urine and feces collection tubes.

30           Procedure. The effects of the experimental compound on body weight, food and water consumption, and fecal and urinary excretion are assessed using the Metabolic Cages. Rats are weighed prior to the assignment to experimental groups.



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Assignment is made using a quasirandom method utilizing pre-assignment body weights to assure that the treatment groups had similar average body weight.

All food is removed from the home cage the night before testing. On the test day, approximately 1 hour prior to dosing, the animals are weighed to the nearest 0.5g. For oral drug administration the animals are dosed with either methyl cellulose (MC) or one dose of experimental compound and returned to their home cage. For intravenous (IV) dosing, the animals are dosed with either PEG-400 or one dose of experimental compound. After the appropriate pretreat time each animal is placed into a Metabolic Cage for a 1 hour test session. Prior to testing, the feeding drawer filled water bottle, are weighed. In addition, the empty feces and urine collection tubes are weighed. Following the test session, the rats are removed from the metabolic cages, weighed, and returned to their home cages. The food and water containers, as well as the feces and urine collection tubes, are then weighed and recorded.

Drugs. For oral dosing experiments, the experimental compound is suspended in 0.5% methyl cellulose (MC). Experimental compound or MC is administered orally (PO) in a dosing volume of 10ml/kg. Drug is made into a homogenous suspension by stirring and ultrasonication. The drug or vehicle suspension is administered 45-60 min prior to test via 6cm piece of polyethylene (PE 90) tubing attached via a Leur lock hub to a 5cc Becton Dickson syringe. For intravenous (IV) dosing, the experimental compound is dissolved in a 50% polyethylene glycol (PEG)-400, 50% distilled water solution. The animals are dosed with either PEG-400 (1 to 4 ml/kg) or one dose of experimental compound (1 to 4 ml/kg) 5 min prior to test.

Statistical Analyses. The means and standard errors of the mean (SEM) for body weight, food consumption, water consumption, fecal excretion, and urinary excretion are presented. One way analysis of variance (ANOVA) is carried out using the Macintosh version of Systat (version 5.2.1). Post-hoc analysis is conducted using the Fisher LSD test. A significant effect is defined as having a p value of <0.05.

The following parameters are defined: Body weight gain is the difference between the body weight of the animal at the time of dosing and the body weight of the animal following dosing. Food consumption is the difference in the weight of the food drawer between dosing and post testing. Water consumption is the

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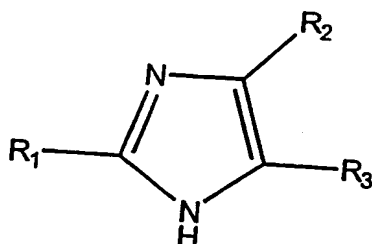
difference in the weight of the water bottle between dosing and post testing.

Fecal excretion is the difference in the weight of the empty fecal collection tube and the weight of the tube post testing. Urinary excretion is the difference in the weight of the empty urinary collection tube and the weight of the tube  
5 post testing.

CLAIMS

1. A pharmaceutical composition for interacting with an NPY5 receptor comprising an amount of a compound of the formula:

5



- 10 or a pharmaceutically acceptable salt

where  $R_1$  is an unsubstituted or mono, di or trisubstituted aryl group wherein said aryl group is mono or bicyclic, in which case only the ring bound to the imidazole ring need be aromatic, and said aryl group is carbocyclic or contain up to 2 hetero atoms which may be nitrogen, oxygen or sulfur and said substituents are

15 individually selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl or alkoxy groups themselves may be substituted by an amino or a mono- or di-alkyl amino group or by a mono- or di-alkaryl amino group or by an acyl group), straight or branched chain

20 lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1 - 6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, an alkyl, aryl or alkaryl amide group, the nitrogen atom of which is bound to the aryl group, mono or di substituted carbamyl wherein the CO group is bound to the aryl ring and

25 each substituent is a lower alkyl or aryl lower alkyl group, mono or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates or any 2 adjacent substituents on the aryl ring may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3;

- 30 one of  $R_2$  and  $R_3$  is selected from the group consisting of hydrogen, hydroxymethyl, alkoxymethyl having up to 6 carbon atoms in each alkoxy group, straight or branched chain lower alkyl having 1-6 carbon atoms, cyano, or a carboxylic

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or carboxylate ester group wherein the esterifying group typically contains up to six carbon atoms;

the other of  $R_2$  and  $R_3$  is an aryl group which is either unsubstituted or mono, di or trisubstituted wherein said aryl groups are mono or bicyclic (in which case only the ring bound to the imidazole ring need be aromatic) and may be carbocyclic or contain up to 2 hetero atoms and said substituents are individually selected from the group consisting of halogen; trihalomethyl; cyano; hydroxy; straight or branched chain lower alkyl having 1-6 carbon atoms; straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl and alkoxy groups themselves may be substituted by an amino group or a mono- or di-alkylamino group, the alkyl groups of which may form a ring together with the nitrogen to which they are bound, or a mono- or di-alkaryl group or by an acyl group or a carbamate); straight or branched chain lower thioalkoxy having 1-6 carbon atoms; acyloxy groups; amino; amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms (said alkyl groups being optionally substituted with a hydroxy or amino group); an alkyl, aryl or alkaryl amide group, the nitrogen atom of which is bound to the aryl group, mono- or di-substituted carbamyl wherein the CO group is bound to the aryl group and the substituents are lower alkyl or aryl lower alkyl; mono- or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group; or mono or diaryl carbamates; additionally any two adjacent substituents on the aryl ring may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1,2 or 3;

and a pharmaceutically acceptable diluent, carrier or solvent.

2. A composition as claimed in claim 1, wherein each aryl group is selected independently from the group consisting of unsubstituted or substituted phenyl, naphthyl, indanyl, pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, indolyl, benzofuranyl, thianaphthyl, isoindolyl, isobenzofuranyl, quinoliny, isoquinoliny, quinazolinyl, indazolyl, quinoxaliny, cinnoliny 1,2,3,4-tetrahydroquinoliny, 2,3-dihydroindolyl, phenomorpholiny, benzodioxaziny, phenothiomorpholiny and methylenedioxyphenyl groups

3. A composition as claimed in claim 2, wherein  $R_1$  is a substituted or unsubstituted phenyl or naphthyl group.

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4. A composition according to claim 2, wherein  $R_1$  is a phenyl, 4-fluorophenyl, pyridin-2-yl or a 2- or 3-thienyl group.
5. A composition according to claim 1, wherein the non-aryl  $R_2$  or  $R_3$  group is selected from hydrogen and, alkyl.
- 5 6. A composition according to claim 1, wherein whichever of  $R_2$  and  $R_3$  is aryl is selected from the group consisting of phenyl, 2- or 3-thienyl, 1,4 benzodioxan-6-yl, benzo[b]morpholinyl, and naphthyl optionally bearing up to three substituents selected from halo, cyano, alkoxy and alkyl groups.
7. A composition according to claim 6, wherein said aryl group bears one  
10 or two substituents selected from the group consisting of alkyl of 1-6 carbon atoms, fluoro, chloro, bromo, cyano and alkoxy of 1 to 6 carbon atoms.
8. A composition according to claim 6, wherein said aryl group bears an N-substituted aminomethyl substituent.
9. A composition according to claim 3, wherein whichever of  $R_2$  and  $R_3$  is  
15 aryl is selected from the group consisting of phenyl, 2- or 3-thienyl, 1,4 benzodioxan-6-yl, benzo[b]morpholinyl, and naphthyl optionally bearing up to three substituents selected from halo, cyano, alkoxy and alkyl groups.
10. A composition according to claim 9, wherein said aryl group bears one  
20 or two substituents selected from the group consisting of alkyl of 1-6 carbon atoms, fluoro, chloro, bromo, cyano and alkoxy of 1 to 6 carbon atoms.
11. A composition according to claim 9, wherein said aryl group bears an N-substituted aminomethyl substituent.
12. A composition according to claim 6, wherein  $R_2$  or  $R_3$  is selected from  
25 the group consisting of 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 4-chlorophenyl, 4-fluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxy-2-fluorophenyl, 4-ethoxy-2-fluorophenyl, 3-fluoro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 3-acetylphenyl, naphthyl, 1,4-benzodioxan-6-yl and benzo [b] morpholinyl, 4-alkyl benzo[b]morpholinyl and 4-alkyl-2H,3H,4H-benzo[e]1,4-thiazinyl.
- 30 13. A composition according to claim 6, wherein  $R_2$  or  $R_3$  is selected from the group consisting of 3-methylaminophenyl, 4-dimethylaminophenyl, 3-ethylaminophenyl, 3-(2-methylbutylaminomethyl)phenyl, 3-(ethylbutyl-

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aminomethyl)phenyl, 3-(1,2-dimethylpropylaminomethyl)phenyl, 3-[(3-cyclohexyl-1-phenylpropyl)methylaminomethyl]phenyl, 3-[(2-cyclohex-1-enylethyl)aminomethyl]phenyl, 3-[(3-methylethoxy)propylaminomethyl]phenyl, 3-(tert.-butylaminomethyl)phenyl, 3-[methyl-(1-phenylpropyl)aminomethyl]phenyl, 3-(methylethylaminomethyl)phenyl and 3-[(4-methylphenyl)methylaminomethyl]phenyl.

14. A composition according to claim 9, wherein  $R_2$  or  $R_3$  is selected from the group consisting of 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 4-chlorophenyl, 4-fluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxy-2-fluorophenyl, 4-ethoxy-2-fluorophenyl, 3-fluoro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 3-acetylphenyl, naphthyl, 1, 4-benzodioxan-6-yl and benzo [b] morpholinyl, 4-alkyl benzo[b]morpholinyl and 4-alkyl-2H,3H,4H-benzo[e]1,4-thiazinyl.

15. A composition according to claim 9, wherein  $R_2$  or  $R_3$  is selected from the group consisting of 3-methylaminophenyl, 4-dimethylaminophenyl, 3-ethylaminophenyl, 3-(2-methylbutylaminomethyl)phenyl, 3-(ethylbutylaminomethyl)phenyl, 3-(1,2-dimethylpropylaminomethyl)phenyl, 3-[(3-cyclohexyl-1-phenylpropyl) methylaminomethyl]phenyl, 3-[(2-cyclohex-1-enylethyl)aminomethyl]phenyl, 3-[(3-methylethoxy)propylaminomethyl]phenyl, 3-(tert.-butylaminomethyl)phenyl, 3-[methyl-(1-phenylpropyl)aminomethyl]phenyl, 3-(methylethylaminomethyl)phenyl and 3-[(4-methylphenyl)methylaminomethyl]phenyl.

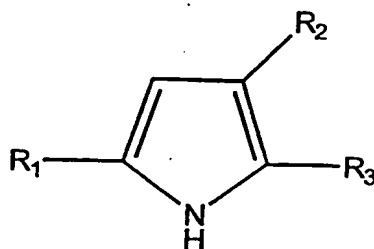
16. A composition according to claim 1, wherein  $R_1$  is a 4-fluorophenyl group.

17. A composition according to claim 1, comprising a diarylimidazole selected from the group consisting of 4-(4-fluorophenyl)-2-phenylimidazole  
 25 2-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene  
 4-ethoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene  
 4-methoxy-3-fluoro-1-(2-phenylimidazol-4-yl)benzene  
 3-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene  
 3-methoxy-1-(2-phenylimidazol-4-yl)benzene  
 30 4-[2-(4-methoxyphenyl)imidazol-4-yl]-1-chlorobenzene  
 4-methoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene  
 4-(4-chlorophenyl)-2-phenylimidazole

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- 4-(4-methylphenyl)-2-phenylimidazole  
4-(4-methoxyphenyl)-2-phenylimidazole  
4-(3-bromophenyl)-2-phenylimidazole  
1-[3-(2-phenylimidazol-4-yl)phenyl]ethan-1-one  
5 4-(4-bromophenyl)-2-phenylimidazole  
4-(3-cyanophenyl)-2-phenylimidazole  
4-(3-cyanophenyl)-2-(4-fluorophenyl)imidazole  
4-(4-cyanophenyl)-2-phenylimidazole  
N-[3-(2-phenylimidazol-4-yl)phenyl]acetamide  
10 2-(4-fluorophenyl)-5-methyl-4-phenylimidazole  
4-[2-(2-fluorophenyl)imidazol-4-yl]-1-chlorobenzene  
4-(2-naphthyl)-2-imidazole  
6-(2-phenylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
6-[(2-(4-fluorophenyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
15 6-[(2-(4-fluorophenyl)-5-methylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin  
6-(2-phenylimidazol-4-yl)benzo[b]morpholine  
4-methyl-6-{2-phenylimidazol-4-yl}benzo[b]morpholine  
4-propyl-7-{2-phenylimidazol-4-yl}benzo[b]morpholine  
6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine  
20 6-[2-(4-fluorophenyl)imidazol-4-yl]-4-methylbenzo[b]morpholine  
4-ethyl-6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine  
4-methyl-6-[2-(4-fluorophenyl)imidazol-4-yl]-2H,3H,4H-benzo[e]1,4-thiazine  
4-(4-chlorophenyl)-2-(2-pyridyl)imidazole  
4-[2-(4-fluorophenyl)imidazol-4-yl]-chlorobenzene  
25 2-indole-3-yl-5-methyl-4-phenylimidazole  
2-[4-(4-chlorophenyl)imidazol-2-yl]thiophene  
[3-(2-phenylimidazol-4-yl)phenyl]methylamine  
dimethyl[3-(2-phenylimidazol-4-yl)phenyl]methylamine  
dimethyl[4-(2-phenylimidazol-4-yl)phenyl]methylamine  
30 ethyl[3-(2-phenylimidazol-4-yl)phenyl]amine  
({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylbutyl)amine  
(ethylbutyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine

- (1,2-dimethylpropyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]methyl}amine  
 (3-cyclohexyl-1-phenylpropyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)methylbutyl)amine  
 (2-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 5 (2-cyclohex-1-enylethyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 (cyclohexylphenylmethyl)methyl{[3-[2-phenylimidazol-5-yl]phenyl]methyl}amine  
 ethyl(1-{3-[2-(4-fluorophenyl)imidazol-5-yl]-isopropyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[3-methylethoxy]propyl]amine  
 (tert-butyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 10 methyl{phenyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine  
 (tert-butyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (methylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[(4-methylphenyl)methyl]amine  
 18. A composition according to claim 1, comprising 2-(4-fluorophenyl)-4-(4-  
 15 methoxyphenyl)imidazole hydrochloride.  
 19. A composition according to claim 1, comprising 2-(2-thien-2-yl)-4-(4-  
 chlorophenyl)imidazole.  
 20. A composition according to claim 1, comprising 2-(4-fluorophenyl)-4-(4-  
 chlorophenyl)imidazole hydrochloride.  
 20 21. A composition according to claim 1, comprising 2-phenyl-4-(3-fluoro-4-  
 methoxyphenyl)imidazole hydrochloride.  
 22. A method of treating conditions susceptible to modulation of NPY  
 receptors which comprises administering to a patient suffering from such conditions an  
 effective dose of a compound of the formula:



or a pharmaceutically acceptable salt

where R<sub>1</sub> is an unsubstituted or mono, di or trisubstituted aryl group



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wherein said aryl group is mono or bicyclic, in which case only the ring bound to the imidazole ring need be aromatic, and said aryl group is carbocyclic or contain up to 2 hetero atoms which may be nitrogen, oxygen or sulfur and said substituents are individually selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl or alkoxy groups themselves may be substituted by an amino or a mono- or di-alkyl amino group or by a mono- or di-alkaryl amino group or by an acyl group), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1 - 6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, alkyl, aryl or alkaryl amide groups, the nitrogen atom of which is bound to the aryl group, mono or disubstituted carbamyl wherein the CO group is bound to the aryl group and wherein each substituent is lower alkyl or aryl lower alkyl, mono or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates or any 2 adjacent substituents bound to the aryl group may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3;

one of  $R_2$  and  $R_3$  is selected from the group consisting of hydrogen, hydroxymethyl, alkoxymethyl having up to 6 carbon atoms in each alkoxy group, straight or branched chain lower alkyl having 1-6 carbon atoms, cyano, or a carboxylic or carboxylate ester group wherein the esterifying group typically contains up to six carbon atoms;

the other of  $R_2$  and  $R_3$  is an aryl group which is either unsubstituted or mono, di or trisubstituted wherein said aryl groups are mono or bicyclic (in which case only the ring bound to the imidazole ring need be aromatic) and may be carbocyclic or contain up to 2 hetero atoms and said substituents are individually selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl and alkoxy groups themselves may be substituted by an amino group or a mono- or di-alkylamino group, the alkyl groups of which together with the nitrogen to which they are bound may form a ring, or a mono- or di-alkaryl

- group or by an acyl group or a carbamate), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms (said alkyl groups being optionally substituted with a hydroxy or amino group), alkyl, aryl and alkaryl amide groups the nitrogen atom of which is bound to the aryl group ,  
 5 mono or disubstituted carbamyl wherein the CO group is bound to the aryl group and wherein each substituent is lower alkyl or aryl lower alkyl, mono- or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates additionally any two adjacent substituents of the aryl group may be  
 10 represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1,2 or 3;
23. A method as claimed in claim 22, wherein said compound is one wherein each aryl group is selected independently from the group consisting of unsubstituted or substituted phenyl, naphthyl, indanyl, pyrrolyl, furanyl, thienyl,  
 15 pyridyl, pyrimidinyl, indolyl, benzofuranyl, thianaphthyl, isoindolyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, quinoxalinyl, cinnolinyl 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydroindolyl, phenomorpholinyl, benzodioxazinyl, phenothiomorpholinyl and methylenedioxyphenyl groups.
24. A method as claimed in claim 22, wherein said compound is one  
 20 wherein  $R_1$  is a substituted or unsubstituted phenyl or naphthyl group.
25. A method according to claim 22, wherein the compound is one wherein  $R_1$  is phenyl or 4-fluorophenyl.
26. A method according to claim 22, wherein one of  $R_2$  and  $R_3$  is hydrogen or methyl and the other is selected from the group consisting of 4-methylphenyl, 3-  
 25 methoxyphenyl, 4-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 4-chlorophenyl, 4-fluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxy-2-fluorophenyl, 4-ethoxy-2-fluorophenyl, 3-fluoro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 3-acetylphenyl, naphthyl, 1, 4-benzodioxan-6-yl and benzo [b] mopholinyl, 4-alkyl benzo[b] morpholinyl and 4-alkyl.-2H,3H,4H-benzo[e]1,4-thiazinyl.
- 30 27. A method according to claim 22, wherein one of  $R_2$  or  $R_3$  is hydrogen or methyl and the other is selected from the group consisting of 3-methylaminophenyl. 4-dimethylaminophenyl, 3-ethylaminophenyl, 3-(2-methylbutylaminomethyl)phenyl, 3-

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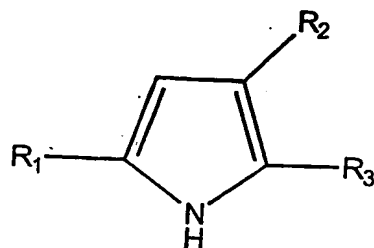
(ethylbutylaminomethyl)phenyl, 3-(1,2-dimethylpropylaminomethyl)phenyl, 3-[(3-cyclohexyl-1-phenylpropyl)methylaminomethyl]phenyl, 3-[(2-cyclohex-1-enylethyl)aminomethyl]phenyl, 3-[(3-methylethoxy)propylaminomethyl]phenyl, 3-(tert.-butylaminomethyl)phenyl, 3-[methyl-(1-phenylpropyl)aminomethyl]phenyl, 3-(methylethylaminomethyl)phenyl and 3-[(4-methylphenyl)methylaminomethyl]phenyl.

28. A method according to claim 22, wherein the compound administered is selected from the group consisting of
- 4-(4-fluorophenyl)-2-phenylimidazole
  - 2-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene
  - 4-ethoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene
  - 10 4-methoxy-3-fluoro-1-(2-phenylimidazol-4-yl)benzene
  - 3-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene
  - 3-methoxy-1-(2-phenylimidazol-4-yl)benzene
  - 4-[2-(4-methoxyphenyl)imidazol-4-yl]-1-chlorobenzene
  - 4-methoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene
  - 15 4-(4-chlorophenyl)-2-phenylimidazole
  - 4-(4-methylphenyl)-2-phenylimidazole
  - 4-(4-methoxyphenyl)-2-phenylimidazole
  - 4-(3-bromophenyl)-2-phenylimidazole
  - 1-[3-(2-phenylimidazol-4-yl)phenyl]ethan-1-one
  - 20 4-(4-bromophenyl)-2-phenylimidazole
  - 4-(3-cyanophenyl)-2-phenylimidazole
  - 4-(3-cyanophenyl)-2-(4-fluorophenyl)imidazole
  - 4-(4-cyanophenyl)-2-phenylimidazole
  - N-[3-(2-phenylimidazol-4-yl)phenyl]acetamide
  - 25 2-(4-fluorophenyl)-5-methyl-4-phenylimidazole
  - 4-[2-(2-fluorophenyl)imidazol-4-yl]-1-chlorobenzene
  - 4-(2-naphthyl)-2-imidazole
  - 6-(2-phenylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin
  - 6-[(2-(4-fluorophenyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin
  - 30 6-[(2-(4-fluorophenyl)-5-methylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin
  - 6-(2-phenylimidazol-4-yl)benzo[b]morpholine
  - 4-methyl-6-{2-phenylimidazol-4-yl)benzo[b]morpholine

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- 4-propyl-7-{2-phenylimidazol-4-yl}benzo[b]morpholine  
 6-[2-(4-fluorophenylimidazol-4-yl)benzo[b]morpholine  
 6-[2-(4-fluorophenylimidazol-4-yl)-4-methylbenzo[b]morpholine  
 4-ethyl-6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine  
 5 4-methyl-6-[2-(4-fluorophenylimidazol-4-yl)-2H,3H,4H-benzo[e]1,4-thiazine  
 4-(4-chlorophenyl-2-(2-pyridyl)imidazole  
 4-[2-(4-fluorophenyl)imidazol-4-yl]-chlorobenzene  
 2-indole-3yl-5-methyl-4-phenylimidazole  
 2-[4-(4-chlorophenyl)imidazol-2-yl]thiophene  
 10 [3-(2-phenylimidazol-4-yl)phenyl]methylamine  
 dimethyl[3-(2-phenylimidazol-4-yl)phenyl]methyl} amine  
 dimethyl[4-(2-phenylimidazol-4-yl)phenyl]methyl} amine  
 ethyl[3-(2-phenylimidazol-4-yl)phenyl]amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylbutyl)amine  
 15 (ethylbutyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 (1,2-dimethylpropyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]methyl}amine  
 (3-cyclohexyl-1-phenylpropyl)methyl{{3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)methylbutyl)amine  
 (2-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl} amine  
 20 (2-cyclohex-1-enylethyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 (cyclohexylphenylmethyl)methyl{{3-[2-phenylimidazol-5-yl]phenyl]methyl} amine  
 ethyl(1-{3-[2-(4-fluorophenyl)imidazol-5-yl]-isopropyl)amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[3-methylethoxy)propyl]amine  
 (tert-butyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine  
 25 methyl{phenyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine  
 (tert-butyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 (methylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[(4-methylphenyl)methyl]amine  
 29. A method as claimed in claim 22, wherein the receptor is an NPY5  
 30 receptor.  
 30. A diarylimidazole of the formula:

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or a pharmaceutically acceptable salt

where  $R_1$  is an unsubstituted or mono, di or trisubstituted aryl group wherein said aryl group is mono or bicyclic, in which case only the ring bound to the imidazole group need be aromatic, and said aryl group is carbocyclic or contain up to 10 2 hetero atoms which may be nitrogen, oxygen or sulfur and said substituents are individually selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl or alkoxy groups themselves may be substituted by an amino or a mono- or di-alkyl amino group or by 15 a mono- or d-alkaryl amino group or by an acyl group or a carbamate), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1 - 6 carbon atoms, said alkyl groups being optionally substituted with a hydroxy or amino group, an alkyl, aryl or alaryl amide group, the nitrogen atom of which is bound to the 20 aryl group, mono or disubstituted carbamyl wherein the CO group is bound to the aryl group and each substituent is lower alkyl or aryl lower alkyl, mono or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates or any 2 adjacent substituents on the aryl ring may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1, 2 or 3;

one of  $R_2$  and  $R_3$  is selected from the group consisting of hydrogen, hydroxymethyl, alkoxymethyl having up to 6 carbon atoms in each alkoxy group, straight or branched chain lower alkyl having 1-6 carbon atoms, cyano, or a carboxylic or carboxylate ester group wherein the esterifying group typically contains up to six 30 carbon atoms;

the other of  $R_2$  and  $R_3$  is an aryl group which is either unsubstituted or mono, di or trisubstituted wherein said aryl groups are mono or bicyclic (in which case

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- only the ring bound to the imidazole group need be aromatic) and may be carbocyclic or contain up to 2 hetero atoms and said substituents are individually selected from the group consisting of halogen, trihalomethyl, cyano, hydroxy, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms (which alkyl and alkoxy groups themselves may be substituted by an amino group or a mono- or di-alkylamino group the alkyl groups of which may form a ring together with the nitrogen to which they are bound, or a mono- or di-alkaryl group or by an acyl group), straight or branched chain lower thioalkoxy having 1-6 carbon atoms, acyloxy groups, amino, amino mono or disubstituted with straight or branched chain lower alkyl having 1-6 carbon atoms (said alkyl groups being optionally substituted with a hydroxy or amino group), an alkyl, aryl, and alkaryl amide groups, the nitrogen atom of which is bound to the aryl group. mono or disubstituted carbamyl wherein the CO group is bound to the aryl group and wherein each substituent is lower alkyl or aryl lower alkyl, mono- or di-alkyl carbamates having up to 6 carbon atoms in each alkyl group or mono or diaryl carbamates additionally any two adjacent substituents of the aryl group may be represented as  $-X-(CH_2)_n-Y-(CH_2)_m-Z-$  where X, Y and Z are either a direct bond, oxygen, sulfur, or NR where R is hydrogen or lower alkyl and n and m are 1,2 or 3; provided that
- 1)  $R_1$  and whichever of  $R_2$  and  $R_3$  is aryl are not both phenyl, a bromophenyl group, a chlorophenyl group, 2,4-dichlorophenyl, a cyanophenyl group, 2-methoxyphenyl, 3-aminophenyl, 4-aminophenyl, 4-trifluormethylphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-acetylaminophenyl, 4-phenoxyphenyl or biphenyl;
  - 2) when  $R_1$  is phenyl, whichever of  $R_2$  and  $R_3$  is aryl is not 2-acetylaminophenyl, chlorophenyl, biphenyl, 4-aminophenyl, p-tolyl, xylyl, 4-methoxyphenyl, 4-dimethylaminophenyl, 4-bromophenyl or 4-hydroxy-2,5-di-tert.-butylphenyl.
  - 3) when one of  $R_2$  or  $R_3$  is phenyl,  $R_1$  is not 2-hydroxyphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 4-chlorophenyl, 4-cyanophenyl, 2,4-xylylphenyl, biphenyl, 2,4-dichlorophenyl or 6-quinolyl; and further provided that

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4)  $R_1$  is not 2-hydroxyphenyl when  $R_2$  or  $R_3$  is p-tolyl,  $R_1$  is not 4-hydroxy-3-methoxyphenyl when  $R_2$  or  $R_3$  is 4-dimethylaminophenyl;  $R_1$  is not 4-hydroxy-3,5-dimethoxyphenyl when  $R_2$  or  $R_3$  is 4-aminophenyl;  $R_1$  is not 4-hydroxy-3,5-di-tert.-butylphenyl when  $R_2$  or  $R_3$  is 4-hydroxyphenyl;  $R_1$  is not 4-chlorophenyl when  $R_2$  or  $R_3$  is 3-trifluorophenyl;  $R_1$  is not 2-hydroxyphenyl when  $R_2$  or  $R_3$  is 2- or 4-acetamidophenyl;  $R_1$  is not 2-methoxyphenyl when  $R_2$  or  $R_3$  is 4-acetamidophenyl;  $R_1$  is not 2-ethoxyphenyl when  $R_2$  or  $R_3$  is 2-acetamidophenyl;  $R_1$  is not 4-methoxyphenyl when  $R_2$  or  $R_3$  is 2-aminophenyl or 2-trifluoromethylphenyl;  $R_1$  is not 2-aminophenyl when  $R_2$  or  $R_3$  is 2-iso-propylcarbamyphenyl or 5-acetamido-2-hydroxyphenyl;  $R_1$  is not 4-dimethylamino when  $R_2$  or  $R_3$  is an ester of 3-methoxy 4-hydroxyphenyl or 3,5-dimethoxy-4-acetoxyphenyl;  $R_1$  is not 2-bromophenyl when  $R_2$  or  $R_3$  is 2,3-xylyl;  $R_1$  is not 2-cyanophenyl when  $R_2$  or  $R_3$  is 4-tolyl; and  $R_1$  is not 3-cyanophenyl when  $R_2$  or  $R_3$  is 4-chlorophenyl..

31. A diaryl imidazole according to claim 30, wherein each aryl group is selected independently from the group consisting of unsubstituted or substituted phenyl, naphthyl, indanyl, pyrroyle, furanyl, thienyl, pyrodyl, pyrimidinyl, indolyl, benzofuranyl, thianaphthyl, isoindolyl, isobenzofuranyl, quinolinyl, isoquinolinyle, quinazolinyl, indazolyl, quinoxalinyl, cinnolinyl 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydroindolyle, phenomorpholinyl, benzodioxazinyl, phenothiomorpholinyl and methylenedioxyphenyl groups

32. A diarylimidazole according to claim 30, wherein  $R_1$  is 4-fluorophenyl.

33. A diarylimidazole according to claim 30, wherein  $R_2$  or  $R_3$  is an N-substituted aminomethylphenyl group.

34. A diarylimidazole according to claim 28, wherein  $R_2$  or  $R_3$  is selected from the group consisting of naphthyl, cyanophenyl, N-substituted benzo[b]morpholine, 2H,3H-benzo[e]1,4-dioxin and N-substituted 2H,3H, 4H-benzo[e]1,4-thiazine

35. A diaryl imidazole selected from the group consisting of:  
 4-(4-fluorophenyl)-2-phenylimidazole;  
 2-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene;  
 4-ethoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene;  
 4-methoxy-3-fluoro-1-(2-phenylimidazol-4-yl)benzene;

- 3-fluoro-4-[2-(4-fluorophenyl)imidazol-4-yl]-1-methoxybenzene;  
3-methoxy-1-(2-phenylimidazol-4-yl)benzene;  
4[2-(4-methoxyphenyl)imidazol-4-yl]-1-chlorobenzene;  
4-methoxy-2-fluoro-1-(2-phenylimidazol-4-yl)benzene;  
5 4-(4-methoxyphenyl)-2-phenylimidazole;  
4-(3-bromophenyl)-2-phenylimidazole;  
1-[3-(2-phenylimidazol-4-yl)phenyl]ethan-1-one;  
4-(3-cyanophenyl)-2-phenylimidazole;  
4-(3-cyanophenyl)-2-(4-fluorophenyl)imidazole;  
10 4-(4-cyanophenyl)-2-phenylimidazole;  
N-[3-(2-phenylimidazol-4-yl)phenyl]acetamide;  
ethyl 2,4-diphenylimidazole-5-carboxylate;  
(2,4-diphenylimidazol-5-yl)methan-1-ol;  
2-(4-fluorophenyl)-5-methyl-4-phenylimidazole;  
15 4-[2-(2-fluorophenyl)imidazol-4-yl]-1-chlorobenzene;  
4-(2-naphthyl)-2-phenylimidazole;  
6-(2-phenylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin;  
6-[(2-(4-fluorophenyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin;  
6-{2-[4-trifluoromethyl]phenyl}imidazol-4-yl}-2H,3H-benzo[e]1,4dioxin;  
20 6-[(2-(4-fluorophenyl)-5-methylimidazol-4-yl)-2H,3H-benzo[e]1,4dioxin;  
6-(2-2-pyridyl)imidazol-4-yl)-2H,3H-benzo[e]1,4dioxin;  
6-(2-phenylimidazol-4-yl)benzo[b]morpholine;  
4-methyl-6-{2-phenylimidazol-4-yl}benzo[b]morpholine;  
4-propyl-7-{2-phenylimidazol-4-yl}benzo[b]morpholine;  
25 6-[2-(4-fluorophenylimidazol-4-yl)benzo[b]morpholine;  
6-[2-(4-fluorophenylimidazol-4-yl)-4-methylbenzo[b]morpholine;  
4-ethyl-6-[2-(4-fluorophenyl)imidazol-4-yl]benzo[b]morpholine;  
6-[2-(4-fluorophenylimidazol-4-yl)-2H,3H,4H-benzo[e]1,4-thiazine;  
4-methyl-6-[2-(4-fluorophenylimidazol-4-yl)-2H,3H,4H-benzo[e]1,4-thiazine;  
30 4-(4-chlorophenyl)-2-(2-pyridyl)imidazole;  
2-[4-(4-chlorophenyl)imidazol-2-yl]pyrazine;  
4-[2-(4-fluorophenyl)imidazol-4-yl]-chlorobenzene;



- 2-indole-3-yl-5-methyl-4-phenylimidazole;  
 2-[4-(4-chlorophenyl)imidazol-2-yl]thiophene;  
 4-(6-chloro(2-pyridyl)-2-phenylimidazole;  
 dimethyl[2-(2-phenylimidazol-4-yl)(4-pyridyl)]amine;  
 5 [3-(2-phenylimidazol-4-yl)phenyl]methylamine;  
 {3-[2-(4-fluorophenyl)imidazol-4-yl]phenyl}methylamine;  
 methyl[3-(2-phenylimidazol-4-yl)phenyl]methylamine;  
 dimethyl[3-(2-phenylimidazol-4-yl)phenyl]methylamine;  
 methyl[4-(2-phenylimidazol-4-yl)phenyl]methylamine;  
 10 dimethyl[4-(2-phenylimidazol-4-yl)phenyl]methylamine;  
 ethyl[3-(2-phenylimidazol-4-yl)phenyl]amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylbutyl)amine;  
 (ethylbutyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine;  
 (1,2-dimethylpropyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]methyl}amine);  
 15 (3-cyclohexyl-1-phenylpropyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)methylbutylamine;  
 (2-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 (2-cyclohex-1-enylethyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine;  
 (cyclohexylphenylmethyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 20 ethyl(1-{3-[2-(4-fluorophenyl)imidazol-5-yl]-isopropyl)amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[3-methylethoxy]propylamine;  
 (tert-butyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)amine;  
 methyl{phenyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine;  
 (tert-butyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 25 (methylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)[(4-methylphenyl)methyl]amine;  
 (cyclohexylphenylmethyl)({3-[2-(4-fluorophenyl)imidazole-5-yl]phenyl}methyl)methylamine;  
 cyclopentyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 30 (methylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)(2-methylpropyl)amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl}methyl)pentylamine;

- ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}(methylethyl)amine;  
 cyclopropyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)amine;  
 cyclobutyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}[2-(4-methylphenyl)ethyl]amine;  
 5 hexyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 (methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}hexylamine;  
 (1,1-dimethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ({3-[2-(4-fluorophenyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 10 (2-cyclohexyl-1-phenylethyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 {[3-(2-phenylimidazol-5-yl)phenyl]methyl}propylamine;  
 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}(2-phenylethyl)amine;  
 (2-cyclopentyl-1-phenylethyl)methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 (2-cyclohex-1-enylethyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 15 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}benzylamine;  
 (ethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 cyclobutyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 (3-methylbutyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 [2-(4-methylphenyl)ethyl]{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 20 (3-cyclohexyl-1-phenylpropyl)({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)methylamine;  
 cyclopropyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 (1,2-dimethylpropyl){[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 ethyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)amine;  
 25 ({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl}(3-methylbutyl)amine;  
 ethyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 cyclohexyl({3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)amine;  
 methyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 pentyl{[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine;  
 30 ([3-[2-(4-fluorophenyl)imidazol-5-yl]phenyl)methyl)dipropylamine and  
 dibutyl[3-(2-phenylimidazol-5-yl)phenyl]methyl}amine.

# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/US 98/13861

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6    A61K31/415    C07D233/64    C07D405/04    C07D413/04    C07D417/04 C07D401/04    C07D405/14    A61K31/44    A61K31/495    A61K31/535 A61K31/54    C07D409/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6    A61K    C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOSEPH G. LOMBARDINO ET AL: "Preparation and antiinflammatory activity of some nonacidic trisubstituted imidazoles " JOURNAL OF MEDICINAL CHEMISTRY., vol. 17, no. 11, 1974, pages 1182-1188, XP002080630 WASHINGTON    US see pages 1184-1185, compound 58	30,35
X	EP 0 257 897 A (FUJISAWA PHARMACEUTICAL CO) 2 March 1988 see claims 1-9	30
A	see page 1, line 10 - line 14; claims 1,11 <div style="text-align: center;">-/-</div>	1
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">14 October 1998</div>		Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">23/10/1998</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-weight: bold;">Henry, J</div>

# INTERNATIONAL SEARCH REPORT

National Application No  
PCT/US 98/13861

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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PCT/US 98/13861

Form PCT/ISA/210 (patent family annex) (July 1992)